AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings include changes to Figure 3-10. These Replacement sheets replace the original sheets of Figures 3-10.

In Figure 3, the unit of footpad swelling has been indicated.

In Figure 4, the unit of footpad swelling has been indicated.

In Figure 5, the unit of footpad swelling has been indicated and the legend amended to remove the second line.

In Figure 6, the unit of tuberculin response has been indicated.

In Figure 7, the unit of footpad swelling has been indicated and the legend amended to remove the third line.

In Figure 8, the unit of footpad swelling has been indicated.

In Figure 9, the unit of footpad swelling has been indicated.

In Figure 10, the unit of footpad swelling has been indicated.

REMARKS

Claims 1-11, 24 and 25 have been cancelled without prejudice. Applicants reserve the right to prosecute the cancelled subject-matter at a later date. Claims 12-13, 15-17, 19, and 22-23 have been amended to correct multiple dependencies. No new matter has been added.

Claims 12-13 and 15-23 are pending. Applicants respectfully request examination of claims 12-13 and 15-23.

SPECIFICATION

The Examiner has objected to the disclosure due to informalities. See Office Action at pages 2-3. For the Examiner's convenience, and due to the nature of the amendments, Applicants provide a clean copy of a substitute specification and a marked up copy of the substitute specification.

Spelling and minor typographical errors have been corrected on page 3, lines 10, 14, and 31, page 11, line 5, page 13, lines 1, 20-21, page 22, line 14, page 24, lines 3 and 5, page 29, line 26, page 36, line 22, page 41, lines 1 and 21, page 42, lines 20 and 22, page 51, line 18, page 52, line 16, page 59, line 27, page 60, lines 19 and 25, page 61, lines 4, 8 and 14, page 62, lines 19 and 26, page 63, fourth box in Table and page 65, line 5.

With respect to the objection regarding the missing units for data in Tables 1 and 2 (on pages 33 and 35 respectively), Applicants have amended the Tables to indicate that the units of measure should be in micrometers. Support for this amendment can be found in Examples 7 and 8 of the specification. With respect to the objection regarding the missing units on page 46, line 25 to page 47, line 13, Applicants have amended the specification on those respective pages to indicate that the units of measure for tuberculin response should be in micrometers. Support for this amendment can be found on page 44, line 5 of the specification. With respect to the objection regarding the missing units on page 50, lines 10-16, Applicants have amended the specification on that page to indicate that the units of measure should be in pixels.

Applicants respectfully request the withdrawal of these objections.

DRAWINGS

The Examiner has objected to Figures 3-10 "because they fail to show the units of swelling." See Office Action at pages 3-4.

In response to the objections, Applicants submit Replacement Sheets for Figures 3-10 that reflect the units of swelling. No new matter has been added. Applicants respectfully request the withdrawal of this objection.

CLAIM OBJECTIONS

The Examiner has objected to claim 13 due to an informality. See Office Action at page 4. Applicants have amended claim 13 to correct the informality. Applicants respectfully request the withdrawal of this objection.

CLAIM REJECTIONS

Rejection of claims under 35 U.S.C. §101

The Examiner has rejected claims 1-4 under 35 U.S.C. §101 as the Examiner contends that "the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101." See Office Action at page 4. In an effort to expedite prosecution and not in acquiescence to the rejection, claims 1-4 have been cancelled thus rendering this rejection moot. Applicants respectfully request the withdrawal of this rejection.

Rejection of claims under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-4 under 35 U.S.C. §112, first paragraph, as the Examiner contends that "since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass." See Office Action at page 5. In an effort to expedite prosecution and not in acquiescence to the rejection, claims 1-4 have been cancelled thus rendering this rejection moot. Applicants respectfully request the withdrawal of this rejection.

The Examiner has rejected claim 14 under 35 U.S.C. §112, second paragraph, as the Examiner contends that "[i]t is unclear what is meant by 'wherein the autoimmune or of the myocardium disease or autoimmune disorder involves." See Office Action at page 5. In an

effort to expedite prosecution and not in acquiescence to the rejection, claim 14 has been cancelled thus rendering this rejection moot. Applicants respectfully request the withdrawal of this rejection.

Rejection of claims under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 12-15 under 35 U.S.C. §112, first paragraph, as the Examiner contends that the specification "does not reasonably provide enablement for the extremely broad scope of the instant claims, i.e., method for treating or preventing any/all autoimmune diseases or disorders. See Office Action at page 5. The Examiner however, acknowledges that the specification is "enabling for: 1) methods of altering thickening of the intimal layers of the common carotid artery of rats following balloon angioplasty utilizing injections of *B. bronchialis, R. coprophilus, T. inchonensis, or M. vaccae,* and 2) altering the levels of BCG skin reactions ...." Id.

In an effort to expedite prosecution and not in acquiescence to the rejection, claim 14 has been cancelled thus rendering this rejection moot. Applicants respectfully request the withdrawal of this rejection with respect to claim 14. Claims 12 and 13 have been amended to incorporate the subject-matter of claim 14. Claim 15 has been amended to depend from claims 12 or 13.

The specification presents data from four of the specifically cited genera that demonstrates that the administration of a whole cell bacteria from one of these genera leads to a decrease in intima thickness in rats. See Examples 10, page 47, line 24 to page 51, line 20 of the specification. Example 10 demonstrates that *Gordonia bronchialis, Rhodococcus coprophilus* and *Tsukamurella inchonensis* were each effective in reducing the intima thickness in rats. See page 50, lines 10-17 of the specification.

A person skilled in the art having been taught that a species from these different genera (i.e., *Gordonia, Rhodococcus* and *Tsukamurella*) were all effective in the reduction of intima thickness, would understand how to treat or prevent an autoimmune disease or an autoimmune disorder or immunize a subject against an autoimmune disease or an autoimmune disorder by administering an effective amount of a pharmaceutical composition and/or immune modulator composition that includes a whole cell of a bacterium from one or more of the genera

Rhodococcus, *Gordonia*, *Nocardia*, *Dietzia*, *Tsukamurella* and *Nocardioides* to a subject wherein the autoimmune disease or autoimmune disorder involves inflammation of the intima of a blood vessel.

As additional support, Applicants further include a copy of a soon to be published paper which discloses that treatment with heat killed bacteria from the genera *Gordonia, Rhodococcus* and *Tsukamurella* inhibits myointimal hyperplasia through immunomodulation. See Attachment A. The paper further provides data demonstrating significant reduction in intima thickness and media thickness

Accordingly, Applicants have informed and demonstrated to a person having ordinary skill in the art how to use the invention commensurate in scope with the claims. Accordingly, the specification adequately enables the claimed methods. Applicants respectfully request reconsideration and withdrawal of this rejection with respect to the remaining claims.

Rejection of claims under 35 U.S.C. §102

The Examiner has rejected claims 1-4 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,599,310 to Matson et al." See Office Action at page 8. In an effort to expedite prosecution and not in acquiescence to the rejection, claims 1-4 have been cancelled thus rendering this rejection moot. Applicants respectfully request the withdrawal of this rejection.

PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Application Serial No. 10/526,228

Claims 12 and 13 have been provisionally rejected under the doctrine of obviousness-type double patenting over claims 18 and 19 of copending Application No. 10/526,228. See Office Action at page 7. Applicants respectfully traverse this rejection.

In an effort to expedite prosecution and not in acquiescence to the rejection, Applicants have amended claims 12 and 13 to incorporate the subject-matter of claim 14. Accordingly, claim 12 now relates to a method for treating or preventing an autoimmune disease or an autoimmune disorder wherein the autoimmune disease or autoimmune disorder involves inflammation of the intima of a blood vessel. Likewise, claim 13 now relates to a method for immunizing a subject against an autoimmune disease or an autoimmune disorder wherein the

autoimmune disease or autoimmune disorder involves inflammation of the intima of a blood vessel.

Accordingly, claims 12 and 13 are patentably distinct from claims 18 and 19 of copending Application No. 10/526,228. Copending Application No. 10/526,228 does not teach or suggest a method of treating or preventing or immunizing against an autoimmune disease or disorder which involves inflammation of the intima of a blood vessel.

As such, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance.

A Supplemental Information Disclosure and Form 1449 is enclosed.

Should any further fees be required by the present Reply, the Commissioner is hereby authorized to charge Deposit Account **19-4293**.

Respectfully submitted,

Date: 6-22-07

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Attachment A

Is Immunotherapy The Future For Prevention Of Myointimal Hyperplasia After Therapeutic Intervention For Atherosclerosis?

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OBJECTIVE: The cytokines secreted by T cells, both in the peripheral circulation and in plaques, can alter the pathological events that occur in human atherosclerosis. Immunotherapy with agents such as heat killed bacteria or heat shock protein 65 can modulate this T-cell induced cytokine response, potentially reducing myointimal hyperplasia. The aim of this study is to assess the effect of novel immunotherapeutic heat killed bacteria on the development of myointimal hyperplasia in a rat carotid balloon trauma model, and to examine the differentiated T cell response by measuring the expression of interferon gamma (Th1) and interleukin-4 (Th2).

METHODS: 75 Sprague-Dawley rats were divided into 5 groups who received intramuscular injection of heat killed bacteria: (i) negative control (ii) Gordonia bronchialis, (iii) Rhodococcus coprophilus, [1] Tsukamurella inchonensis or (v) Mycobacterium vaccae. After 56 days they underwent balloon trauma to the left common carotid artery. The rats were sacrificed after 70 days and the carotid arteries assessed for the development of myointimal hyperplasia. Blood was taken for cytokine analysis at 49 and 70 days. Statistical analysis was performed using a Mann-Whitney U test and the McNemar test for analysis of the cytokine response to each immunotherapeutic agent.

RESULTS: There was a significant reduction in intima/media ratio in all the rats treated by immunomodulation versus the negative controls (0.91+/-0.05 vs 0.52+/-0.03 vs 0.60+/-0.03 vs 0.43+/-0.03 vs 0.37+/-0.03; $p<0.001$). Post balloon trauma G. bronchialis increased mRNA IFN-γ ($p<0.02$) and reduced mRNA IL-4 ($p<0.05$). R. coprophilus, T. inchonensis and M. vaccae significantly increased production of mRNA IFN-γ ($p<0.001$). R. coprophilus and M. vaccae also decreased production of

mRNA IL-4 (R.coprophilus $p<0.05$, M.vaccae $p<0.01$). In addition, rats treated with M. vaccae demonstrated a significant increase in mRNA IL-4 from inoculation alone ($p<0.01$). There was a significant difference in the number of positive results between day 49 and day70 for mRNA IFN-γ in rats given R. coprophilus, T. inchonensis and M. vaccae ($p<0.01$), and for mRNA IL-4 for R. coprophilus and T. inchonensis alone ($p<0.01$).

CONCLUSION: Treatment with heat-killed bacteria inhibits myointimal hyperplasia through immunomodulation and may provide a novel therapeutic option to prevent restenosis.

Keywords: myointimal hyperplasia, bacterial vaccines, heat shock protein, cytokines, rats

Introduction

Atherosclerosis is the leading cause of death in the Western world. It leads to myocardial infarction, limb loss and strokes. Inflammation is now linked to the progression of atherosclerotic vascular disease. Vascular injury, naturally by spontaneous plaque rupture, or iatrogenically secondary to arterial interventions such as angioplasty or bypass surgery, stimulates inflammatory responses that may adversely affect healing leading to a related process – myointimal hyperplasia (MIH). In contrast to atherosclerosis, MIH occurs rapidly, developing in 14 days in rats and within 3 months in humans[2]. In response to cytokines and growth factors released after vessel wall injury, vascular smooth muscle cells (VSMC) undergo a phenotypic change becoming more secretory, proliferating and migrating to the intima leading to vessel or graft stenosis[3]. The differential production of cytokines by T-helper cells determines the nature and extent of this response[4]. The antigens which initiate this inflammatory response are hypothesised to be proteins produced by mitochondria within endothelial cells known as heat shock protein family (hsp). Many bacteria show cross-reactivity to these human stress proteins and have an immunomodulatory effect on specific aspects of the T cell response, by down-regulating either the Th2 or Th1 response[5,6]. We have previously shown that Mycobacterium vaccae immunisation was able to reduce MIH in an animal model[7]. The aim of the current study was to investigate the effect of immunomodulation on the generation of MIH using alternative bacterial preparations in the same animal model and correlate this with changes in T-helper cell cytokine production.

Methods

All experiments were conducted in accordance with the Animals (Scientific Procedures) Act 1986 and UK guidelines. Male Sprague-Dawley rats (350-400g) were housed in standard conditions with a 12 hour light/dark cycle and access to water and food ad libitum. A power calculation was performed based on the standard deviation of the generation of MIH in the rat balloon trauma model of 0.18, applying a 2-tailed significance of 0.05 and requiring a 95% power to detect a 25% difference would require group sizes of n=15.

Four species from genera of Actinomycetales were cultured on an antigen-free medium (modified Sauton's) and harvested into borate buffered (pH 8.0) physiological saline. Master suspensions of each were prepared at 10^{10} bacilli/ml and preparations were sterilised by autoclaving.

The rats were divided into 5 groups: Group 1 (control)– Borate buffered saline at pH 8 alone; Group 2 – Gordonia bronchialis (G.bronchialis); Group 3 – Rhodococcus coprophilus (R.coprophilus); Group 4 – Tsukamurella inchonensis (T.inchonensis); Group 5 – Mycobacterium vaccae (M.vaccae). All rats were inoculated by subcutaneous injection to their flank on days 0 and 21. All active inoculations contained $5x10^8$ heat killed bacteria at initial inoculation and $10x10^8$ at second inoculation. Blood samples were taken for analysis of IFN-γ (Th1) and IL-4 (Th2) on days 49 and 70. The rats underwent balloon trauma on day 56.

(i) Balloon trauma technique

Briefly, the rats were anaesthetised by intra-peritoneal injection of diazepam and intramuscular hypnorm (Janssen, Beerse, Belgium) and a left common carotid

angioplasty was performed under aseptic conditions: After an anterior midline incision in the neck, the common carotid artery was identified and cleared of adherent tissue to allow a clip to be applied around it without causing crush injury to the vagus nerve or the associated superior cervical ganglion and sympathetic chain. After temporary cessation of carotid artery blood flow a 2 Fr Fogarty arterial embolectomy catheter (BVM, Medical Limited, Leicester, UK) was inserted into the lumen of the left external carotid artery. Once in position the catheter was guided to a fixed distance (5 cm) down the external and common carotid artery to a point such that the catheter was adjacent to the aortic arch. Once in position the balloon was inflated with fluid sufficient to generate slight resistance within the vessel wall (0.3mls), and the catheter was withdrawn. With the balloon inflated, the catheter was withdrawn at a steady rate (approx. 2 cm/sec) back to a point proximal to the point of insertion. This procedure was repeated a total of three times. Then the catheter was removed and the external carotid ligated and the wound closed. The animals were then allowed to recover and returned to their cages.

(ii) Histology and morphometric analysis

Fourteen days after balloon trauma was carried out the rats were sacrificed by anaesthesia and terminal exsanguination by cardiac puncture. The neck wound was reopened and both CCA and bifurcations were removed en bloc after careful surgical exposure. The arteries were flushed with heparinised saline and then fixed overnight in formalin 20%. All tissue was embedded in paraffin blocks and 5μm transverse sections taken. The sections were stained using Verhoeff-van Gieson's stain for elastin (Figure 1). Intimal, medial and luminal areas were measured using Scion software (Scioncorp, Maryland, USA). The ratio of medial to intimal area was

calculated and the mean of 5 measurements taken from 3 sequential sections was taken for each animal. Results were expressed as the mean +/- SEM of the intima/media ratio (MIH).

(iii) Blood sample analysis

Blood was taken from the tail vein on Day 49 and by terminal exsanguination by cardiac puncture on Day 70.

Samples were taken into 'Quiagen' tubes and stored at -20°C until all were analysed at the end of the study. The 'Paxgene system' was used to determine the messenger RNA for IFN-γ and IL-4.

Statistical analysis

Results are expressed as means +/- SEM. Comparisons between the groups were made using the chi square and Fisher's exact test for categorical variables and Kruskall-Wallis and Mann-Whitney U tests for quantitative measurements. Within group comparisons were performed by the McNemar and Wilcoxon signed rank tests. Statistical significance was inferred at $p<0.05$.

Results

All of the rats survived the procedure and appeared to tolerate the inoculations well, as evidenced by steady weight gain (results not shown). However, several histological specimens were lost during processing, in 3 cases no tissue found after paraffin embedding and in 5 cases inadequate sectioning and staining such that sufficient measurements could not be made (from rats 2, 11, 13, 14 (Group 1); rat 35 (Group 3); rats 46, 50 and 57 (Group 4)). Therefore for morphometric analysis, Group 1 n= 11, Group 2 n=15, Group 3 n=14, Group 4 n=12 and Group 5 n=15. Blood analysis was complete for all but sample for Group 5 Day 70, which was lost in transport.

(i) Development of MIH (Figure 2)

All of the groups demonstrated significantly reduced stimulation of MIH from control ($p<0.001$).

The data was also analysed for between group differences. The rats given R.coprophilus and G.bronchialis developed significantly more MIH than the other treatment groups ($p<0.05$), with no significant difference between these 2 treatment groups ($p=0.10$). Likewise, the rats given T.inchonensis and M.vaccae showed a similar inhibitory effect on the development of MIH with no significant difference between them ($p=0.31$).

(ii) Blood analyses

The method of analysis for mRNA for IFN-γ, a Th1 cytokine and IL-4, a Th2 cytokine applied a threshold. Tables 1 and 2 show the number of samples which demonstrated positive results (levels greater than threshold) for each day and analysis performed and the mean ± SEM for the positive samples.

Using the McNemar test there was a significant difference in the number of positive results between day 49 and day70 for mRNA IFN-γ in rats given R.coprophilus, T.inchonensis and M.vaccae ($p<0.01$), and for mRNA IL-4 for R.coprophilus and T.inchonensis alone ($p<0.01$).

There was no statistical difference among the groups when levels of mRNA IFN-γ were assessed at day 49, however post balloon therapy, at day 70 levels were significantly different from control in all bacteria-treated groups, as was the amount of positive results. In addition, there was a significant increase in the expression of mRNA IFN-γ in all groups treated with bacteria between days 49 and 70 (G.bronchialis $p=0.02$, R.coprophilus $p<0.001$, T.inchonensis $p<0.001$, M.vaccae $p<0.001$).

At initial assessment on day 49 the levels of mRNA IL-4 in rats treated with M.vaccae were significantly higher than control ($p<0.01$). At day 70 levels were significantly different from control in groups treated with G.bronchialis, R.coprophilus, T.inchonensis and M.vaccae ($p<0.035$). There was a significant reduction in mRNA IL-4 levels pre and post balloon trauma in the control group ($p<0.04$) and the groups treated with G.bronchialis ($p<0.05$), R.coprophilus ($p<0.05$) and M.vaccae ($p<0.01$).

Overall post balloon trauma G.bronchialis stimulated an increase in mRNA for IFN-γ, and reduced the mRNA for IL-4. Both R.coprophilus and T.inchonensis significantly increased production of IFN-γ and decreased production of IL-4. In rats treated with

M.vaccae there was also a significant increase in production of IFN-γ after balloon trauma. However, there was a significant increase in IL-4 from inoculation alone. After balloon trauma there was a significant decrease in production of IL-4 consistent with that of the previous 2 treated groups.

Discussion

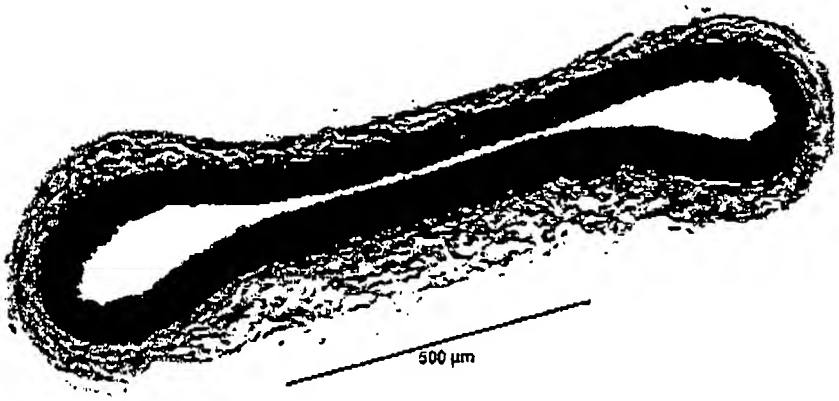
This study has shown that immunomodulation with heat killed bacterial preparations can reduce the development of MIH in the rat carotid by approximately 50% over control. This was accompanied by changes in the T-helper cell cytokine profile suggestive of a predominant Th1 cytokine response with the major increase being in IFN-γ[8]. All of the 4 organisms studied were effective, but T.inchonensis and M.vaccae were the most promising candidates for further study. This confirms our previous report that M.vaccae reduces MIH in the same model, but additionally demonstrates the associated T-cell cytokine changes as well as the effect of the other heat killed bacteria[7 9-11]. All the agents have been used in human pilot studies and appear safe (unpublished data) and M.vaccae has been used extensively in clinical trials of immunotherapy for other indications[12-14].

There is evidence to suggest that the cytokines secreted by T-cells can modulate the pathological cellular events that occur in the development of atherosclerosis, where there is also VSMC migration and proliferation[15 16]. In particular IFN-γ appears to play a central role[15]. However, the role of the T-cell in initiating the cytokine cascade in MIH has been less well explored. Xu[17] demonstrated that levels of serum antibodies to hsp65 were significantly increased in subjects who were found to have sonographic evidence of carotid atherosclerotic lesions versus those without. Whilst our own unit has shown elevated levels of antibodies to hsp70 in patients with intermittent claudication, critical lower limb ischaemia or abdominal aortic aneurysms[18]. An acceleration of fatty streak formation in mice, and an increase in carotid MIH in rats has also been shown after immunisation with mycobacterial hsp65[19 20]. Mycobacteria express cell surface proteins that have >50% amino acid homology with human hsp60/65[21]. Immunotherapy with mycobacterium species

appears to induce a Th1-dominant cell-mediated response to stress or trauma [9 22]. Our hypothesis is that tissue inflammation after balloon trauma is initiated or maintained by cell mediated immunity based against the expressed hsp on the surface of vascular wall cells. Such responses have been shown to be involved in several autoimmune conditions. This response is presumably reduced by immunotherapy such as investigated in the current study.

It has been demonstrated in an animal model that T lymphocyte depletion results in larger proliferative lesions after catheter denudation[23]. In addition there are several other disease models where the greatest immunopathology is seen when a mixture of Th1 and Th2 cytokines is released into the lesion[24 25]. Indeed in the current study we also saw a fall in the mRNA for the Th2 cytokine IL-4 after balloon trauma alone, which appeared to be enhanced by our immunotherapy. It is more likely that it is the combination of aggravated Th1 and attenuated Th2 response which resulted in our findings. However, the Th1/Th2 paradigm cannot by itself explain the pathogenesis of MIH.

Immunotherapy is an exciting novel treatment for MIH that could significantly improve outcomes after bypass surgery and angioplasty. However, more research is needed to understand the exact mechanisms that induce the response we have observed, to assess the reproducibility of the treatment in both the patient population and individuals, and the longevity of the response.



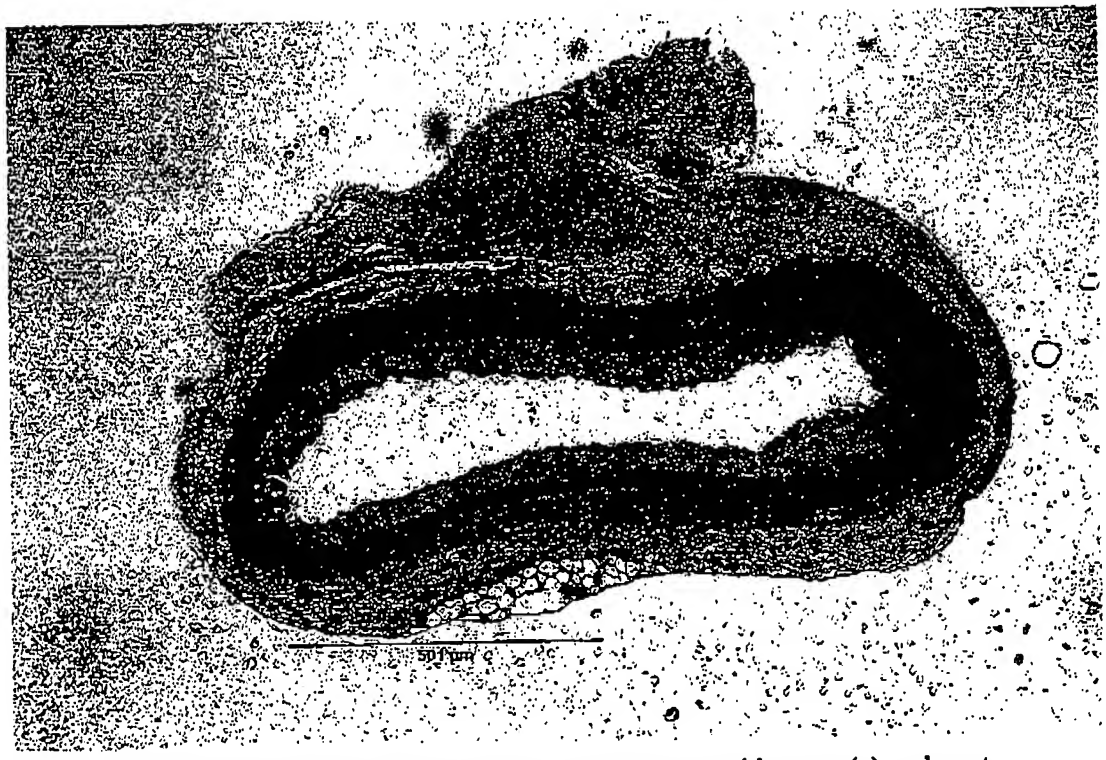


Figure 1. Photomicrographs (x40) showing a normal rat carotid artery (a) and a rat carotid artery demonstrating myointimal hyperplasia (b) (grey area).

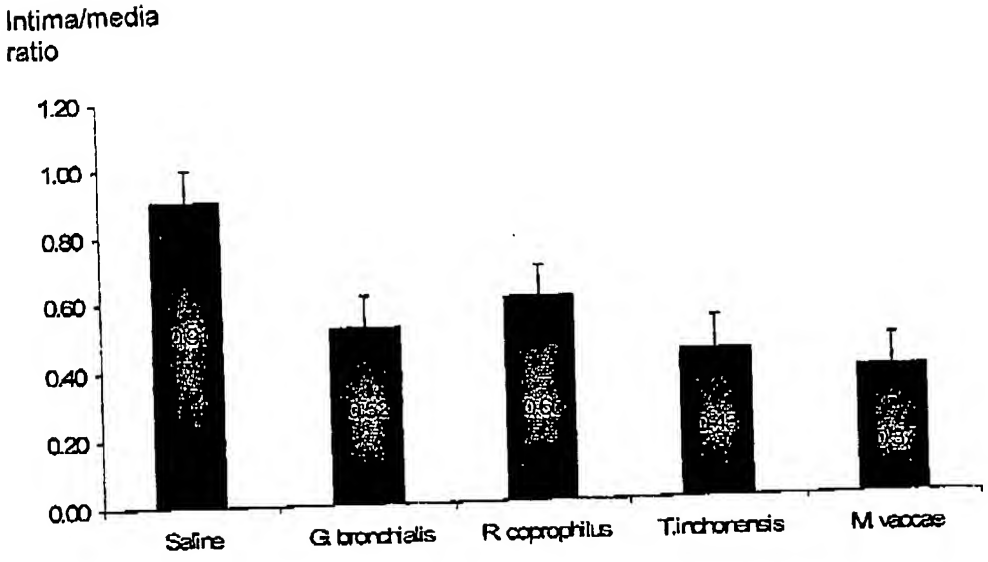


Figure 2: Graph demonstrating the mean and SEM of the MIH generated as measured by intima/media ratio in each group. The mean of 5 measurements from 3 sequential sections from each rat were analysed. (S n=11, G.b. n=15, R.c. n=14, T.i. n=12, M.v. n=15).

Saline group significantly different from the treated groups ($p<0.001$)

R. c. group significantly different from the other treated groups ($p<0.05$)

	Positive samples	Day 49	Positive samples	Day 70
Control	6/15	1014±411	8/15♦	1796±1196$
Gordonia bronchialis	7/15	1184±559	11/15	21127±8233#
Rhodococcus coprophilus	1/15	186	15/15*	25121±13030#
Tsukamurella inchonensis	4/15	714±388	15/15*	12292±3470#
Mycobacterium vaccae	4/15	2067±1317	14/14*	13976±2992#

Table 1: Table showing the number of samples with greater than threshold concentrations for mRNA for IFN-γ and the mean and SEM of the positive analyses for samples taken at Day 49 (pre-balloon trauma) and Day 70 (post-balloon trauma).

♦ significantly different from remaining groups ($p<0.001$, chi square and Fisher's exact test)

$ significantly different from remaining groups ($p<0.015$, Kruskall-Wallis analysis of variance)

* significantly different from results obtained at Day 49 ($p<0.01$, McNemar test)

significantly different from results obtained at Day 49 (Wilcoxon test, G.b. $p<0.02$, R.c./T.i./M.v. $p<0.001$)

	Positive samples	Day 49	Positive samples	Day 70
Control	5/15	74.3±32.8	3/15♦	0.38±0.22#
Gordonia bronchialis	6/15	241±115	5/15♦	11.74±5.05#
Rhodococcus coprophilus	2/15	122±88.5	15/15*	61.6±32.7
Tsukamurella inchonensis	2/15	37.8±28.5	15/15*	38.8±7.19#
Mycobacterium vaccae	10/15	779±365$	14/14	36.9±6.98#

Table 2: Table showing the number of samples with greater than threshold concentrations for mRNA for IL-4 and the mean and SEM of the positive analyses for samples taken at Day 49 (pre-balloon trauma) and Day 70 (post-balloon trauma).

♦ significantly different from remaining groups ($p<0.001$, chi square and Fisher's exact test)

$ significantly different from remaining groups ($p<0.01$, Kruskall-Wallis analysis of variance)

* significantly different from results obtained at Day 49 ($p<0.01$, McNemar test)

significantly different from results obtained at Day 49 (Wilcoxon test, control $p<0.04$, G.b. $p<0.05$, R.c. $p<0.05$, M.v. $p<0.01$)

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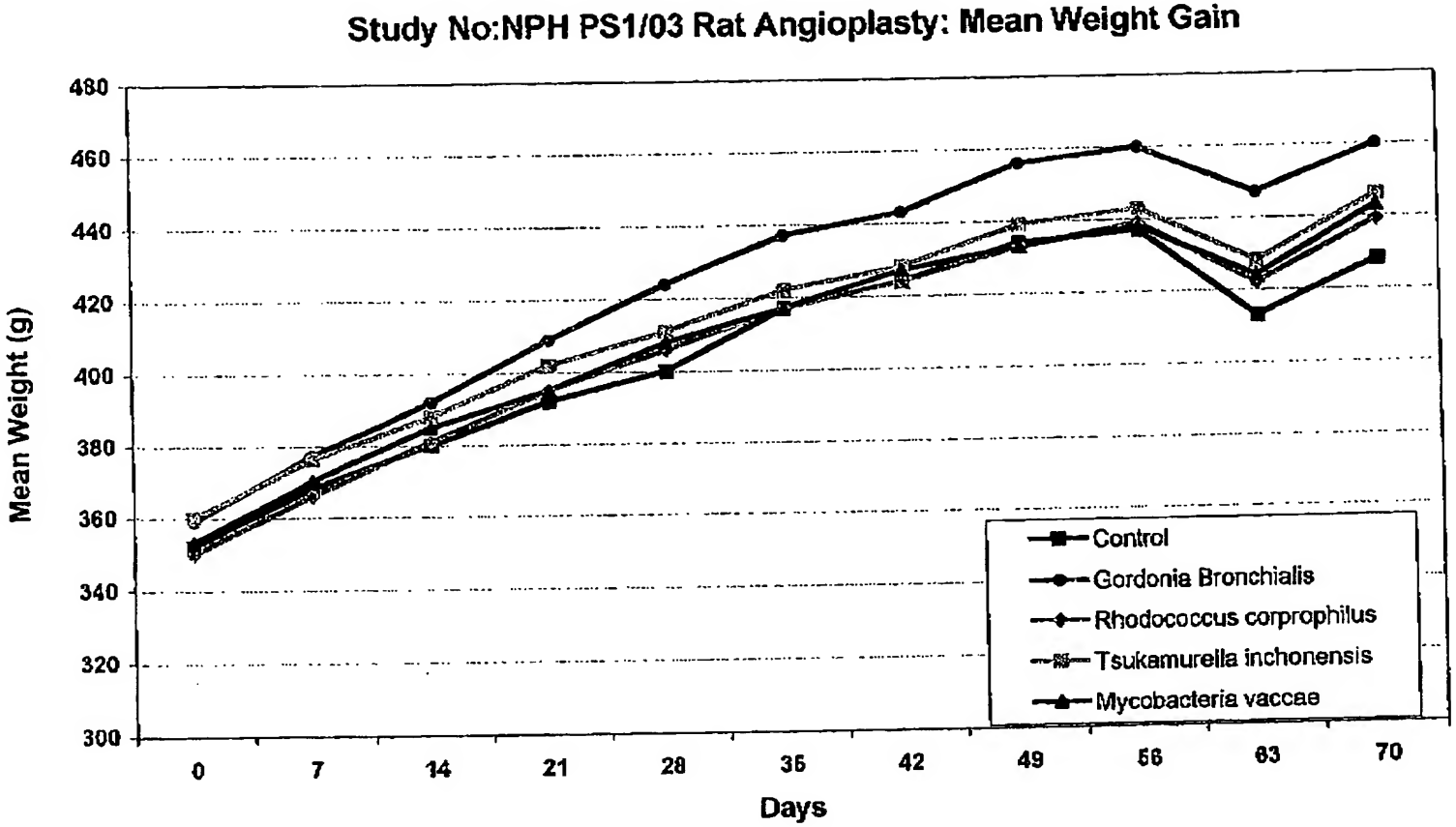
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21
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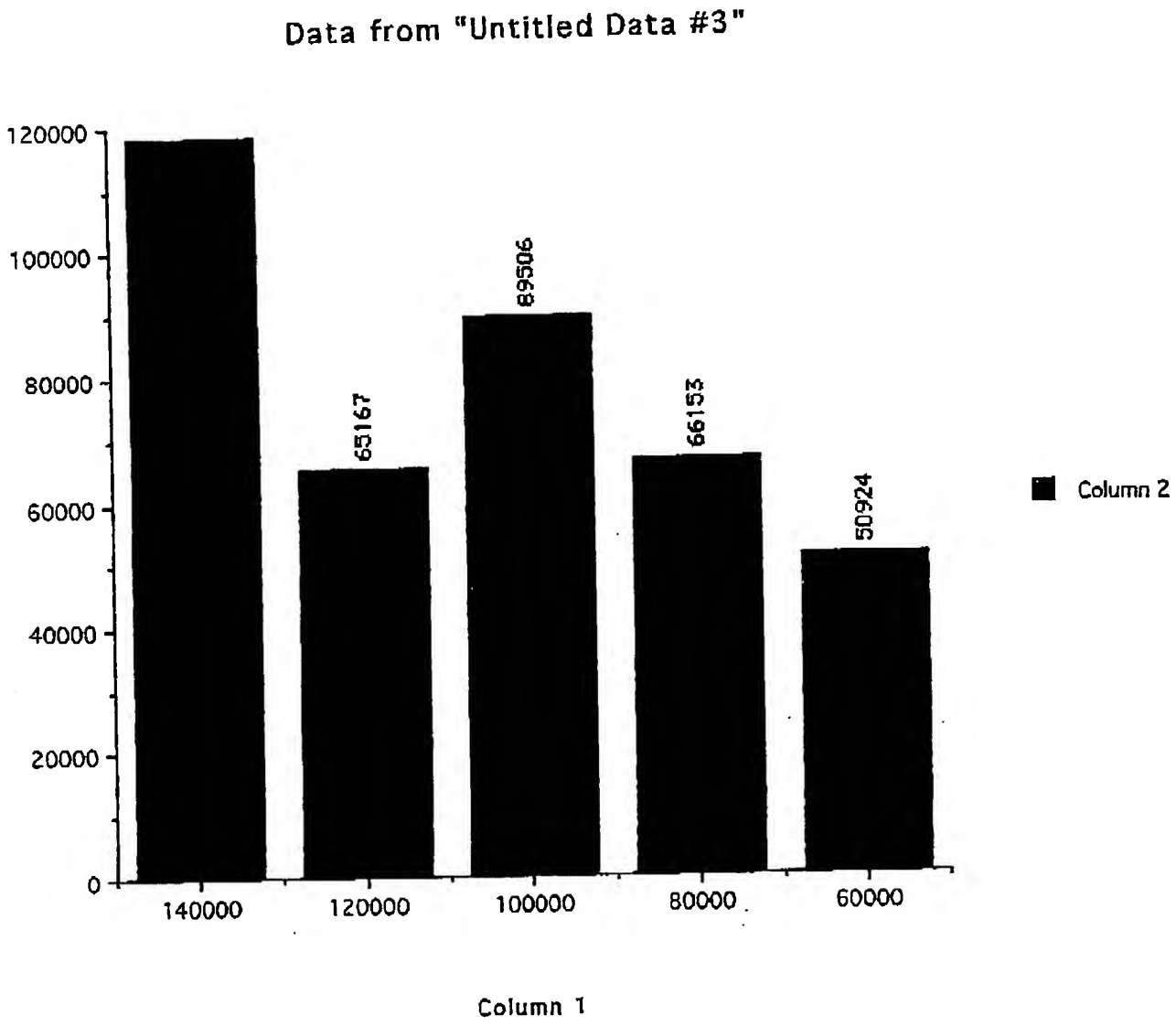
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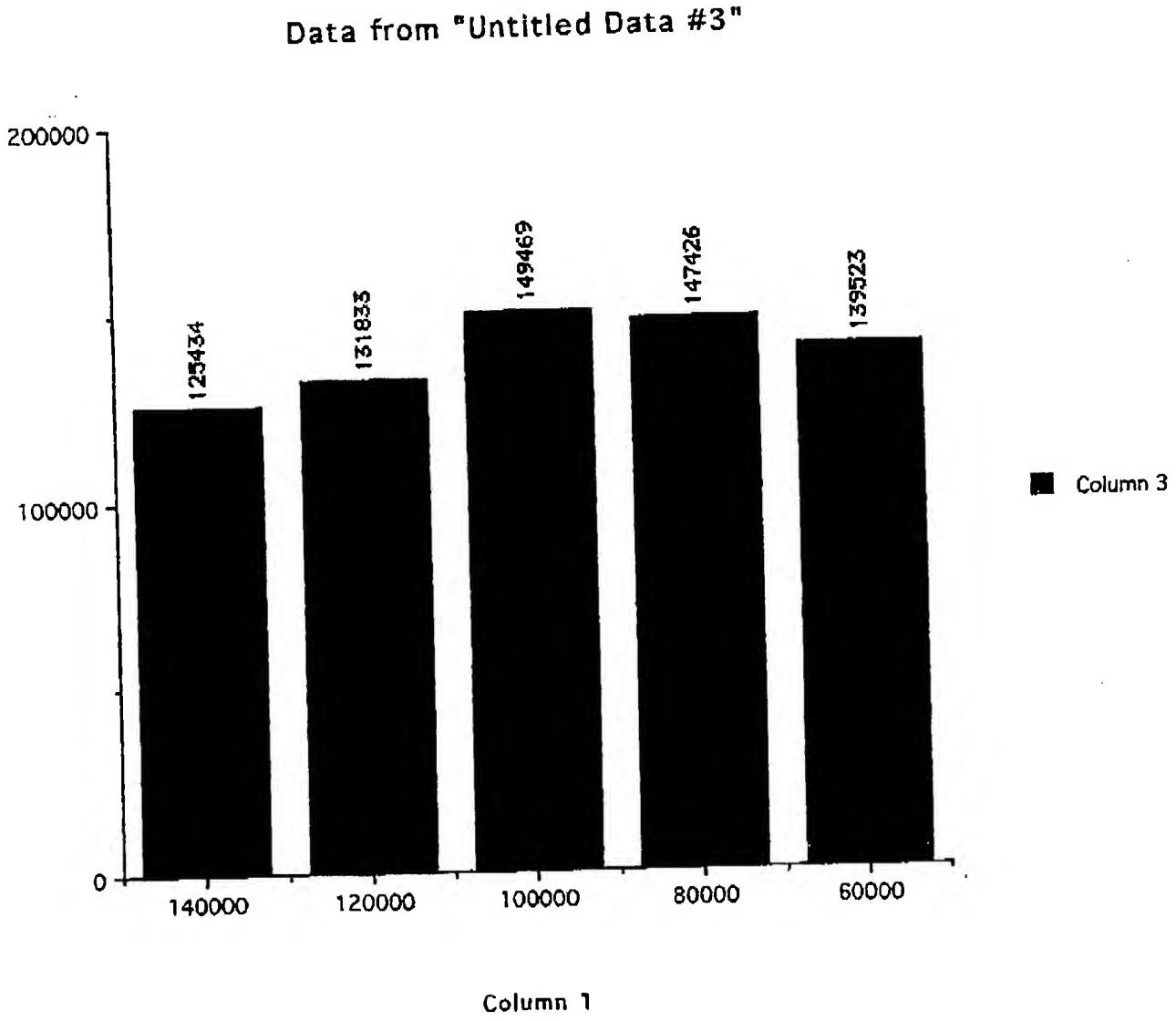
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